Neurosurg Rev (2016) 39:401–409
DOI 10.1007/s10143-015-0698-z

ORIGINAL ARTICLE

The influence of intraoperative resection control modalities on survival following gross total resection of glioblastoma

Marian C. Neidert[1] · Isabel C. Hostettler[1] · Jan-Karl Burkhardt[1] · Malte Mohme[1] · Ulrike Held[2] · Reto Kofmehl[2] · Günter Eisele[3] · Christoph M. Woernle[1] · Luca Regli[1] · Oliver Bozinov[1]

Received: 2 May 2015 / Revised: 25 September 2015 / Accepted: 31 October 2015 / Published online: 9 February 2016
© Springer-Verlag Berlin Heidelberg 2016

Abstract The purpose of the present study is to analyze the impact of intraoperative resection control modalities on overall survival (OS) and progression-free survival (PFS) following gross total resection (GTR) of glioblastoma. We analyzed data of 76 glioblastoma patients (30f, mean age 57.4 ± 11.6 years) operated at our institution between 2009 and 2012. Patients were only included if GTR was achieved as judged by early postoperative high-field MRI. Intraoperative technical resection control modalities comprised intraoperative ultrasound (ioUS, $n = 48$), intraoperative low-field MRI (ioMRI, $n = 22$), and a control group without either modality ($n = 11$). The primary endpoint of our study was OS, and the secondary endpoint was PFS—both analyzed in Kaplan-Meier plots and Cox proportional hazards models. Median OS in all 76 glioblastoma patients after GTR was 20.4 months (95 % confidence interval (CI) 18.5–29.0)—median OS in patients where GTR was achieved using ioUS was prolonged (21.9 months) compared to those without ioUS usage (18.8 months). A multiple Cox model adjusting for age, preop Karnofsky performance status, tumor volume, and the use of 5-aminolevulinic acid showed a beneficial effect of ioUS use, and the estimated hazard ratio was 0.63 (95 % CI 0.31–1.2, $p = 0.18$) in favor of ioUS, however not reaching statistical significance. A similar effect was found for PFS (hazard ratio 0.59, $p = 0.072$). GTR of glioblastoma performed with ioUS guidance was associated with prolonged OS and PFS. IoUS should be compared to other resection control devices in larger patient cohorts.

Keywords Glioblastoma · Intraoperative magnetic resonance imaging · ioMRI · Intraoperative ultrasound · ioUS · Survival

Introduction

With an incidence of 2–3/100,000 people per year in Europe and the USA (www.cbtrus.org), glioblastoma is the most frequent and malignant primary brain tumor in adults [17]. Due to the infiltrative nature of this disease, surgery fails to remove the entire tumor cell population, and despite a postoperative combination of radiotherapy and chemotherapy, overall survival (OS) is poor with a median OS of 14.6 months [30, 31].

Regarding surgery for malignant brain tumors, gross total resection (GTR) is associated with longer survival than subtotal resection or biopsy [1, 13, 16, 18, 23, 29, 35, 36]. One of the main challenges in achieving the largest extent of resection (EOR) without causing damage to the surrounding functional brain parenchyma is the distinction between tumor and normal brain. This distinction is especially difficult in primary brain tumors, which often show a diffuse growth pattern resulting in a transitional zone at the tumor margins where malignant and normal cells are intermingled. Much effort has been invested in the development of technologies that might improve EOR

Marian C. Neidert and Isabel C. Hostettler contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s10143-015-0698-z) contains supplementary material, which is available to authorized users.

✉ Oliver Bozinov
oliver.bozinov@usz.ch

[1] Department of Neurosurgery, University Hospital, University of Zurich, Frauenklinikstr.10, 8091, Zurich, Switzerland

[2] Horten Centre for Patient Oriented Research and Knowledge Transfer, University of Zurich, Zurich, Switzerland

[3] Department of Neurology, University Hospital, University of Zurich, Zurich, Switzerland

and that might help to distinguish tumor from normal brain. In daily practice, neuronavigation, intraoperative magnetic resonance imaging (ioMRI), intraoperative ultrasound (ioUS), intraoperative computed tomography (ioCT), and 5-aminolevulinic acid (5-ALA) are the most frequently used ones.

This study includes only patients who had microsurgical GTR (GTR; here defined by no residual nodular contrast enhancement in the early postoperative MRI within 72 h). This study does not aim to analyze the impact of intraoperative resection control modalities on EOR. We investigate whether OS and progression-free survival (PFS) in these patients might depend on the intraoperative imaging modality used to achieve GTR.

Patients and methods

Medical charts of patients with primary glioblastoma operated at our institution between the years 2009 and 2012 were reviewed retrospectively. According to federal regulations, no written informed consent was required for this study. A waiver was obtained from the local ethics committee (KEK-StV-Nr. 27/14). We included data of patients with GTR of these lesions as evaluated by an independent neuroradiologist in the early postoperative MRI, defined as cerebral MRI with contrast within 72 h after surgery. We excluded patients with residual tumor (defined by residual nodular contrast enhancement) in the early postoperative magnetic resonance imaging (MRI), as well as patients followed for less than 6 months. The primary endpoint of this study was OS depending on which intraoperative resection device was used, and the secondary endpoint was PFS as defined by radiographic recurrence. Intraoperative technical resection control modalities comprised ioUS and ioMRI and a group of patients without intraoperative resection control (only neuronavigation, which was used in all cases). We used a small-range high-frequency (7–15 MHz) ioUS probe (L15-7 probe iU22 Ultrasound Systems, Philips, Bothell, USA) as shown in our previous publications [7, 26] as well as in an illustrative case (Fig. 1) and a low-field ioMRI, PoleStar N-20 0.15 T (until 09/2010) and N-30 0.15 T (after 09/2010; both Medtronic, Louisville, USA). In addition, we assessed whether 5-ALA (Gliolan®, medac Hamburg, Germany) was used. Tumor volume was calculated using measurements of the contrast-enhancing rim on gadolinium-enhanced T1-weighted MR images and applying the formula: tumor volume $= 4/3 * p * 1/2x * 1/2y * 1/2z$), where x, y, and z are the maximum diameters within the three axes.

Statistical analysis

Descriptive statistics were used to present continuous variables as mean with standard deviation and categorical variables as counts and percentages of total. OS and PFS are presented as median and 95 % confidence interval (CI). Continuous variables were compared between groups using the Mann-Whitney test, and categorical variables were compared using the Fisher's exact test.

The primary endpoint OS was first addressed graphically using Kaplan-Meier plots. To quantify the effect of the intraoperative imaging device (ultrasound versus no ultrasound) on survival, we fitted a multiple Cox proportional hazards model. The association between the imaging device and the outcome was adjusted for the effect of the potential confounders age, 5-ALA, tumor volume, and preoperative Karnofsky performance status. After fitting this model to the full dataset, we performed additional subgroup analyses within the patients with glioblastoma.

The level of statistical significance was set at 5 %. Statistical analyses were performed using SPSS 20 (IBM, Chicago, IL, USA) and R (R Core Team (2013). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

Results

Patients

We included data of 76 glioblastoma patients (30 females [39.5 %], 46 males [60.5 %], mean age 57.4 ± 11.6 years) with GTR and adequate follow-up. The mean follow-up time was 623.8 ± 346 days. 5-ALA was used in 19 (25 %) glioblastoma cases. Intraoperative technical resection control modalities comprised ioUS ($n = 48$), ioMRI ($n = 22$), and a control group without either modality ($n = 11$). In five cases, both ioUS and ioMRI were used. Basic patient characteristics are shown in Table 1. The overlap of different technical resection devices and 5-ALA is shown in a VENN diagram (supplementary Fig. S1).

Primary endpoint—OS

OS is illustrated in a graphical approach using Kaplan-Meier plots for all patients ($n = 76$) as depicted in Fig. 2a. When looking at the use of intraoperative resection control devices (Fig. 2b), OS was longer in patients with ioUS (either ioUS alone or ioUS in combination with ioMRI). Thus, in further graphical and statistical analyses, we focused on the comparison between patients that had GTR with ioUS compared to those without ioUS. Median OS for all patients ($n = 76$) was 20.4 months (95 % CI 18.5–29.0) as depicted in Fig. 2a. In the group of glioblastoma patients with ioUS ($n = 48$), median OS was 21.9 months (95 % CI 18.5–33.1)—30 patients died during follow-up (see Fig. 3a). In contrast to that, median OS

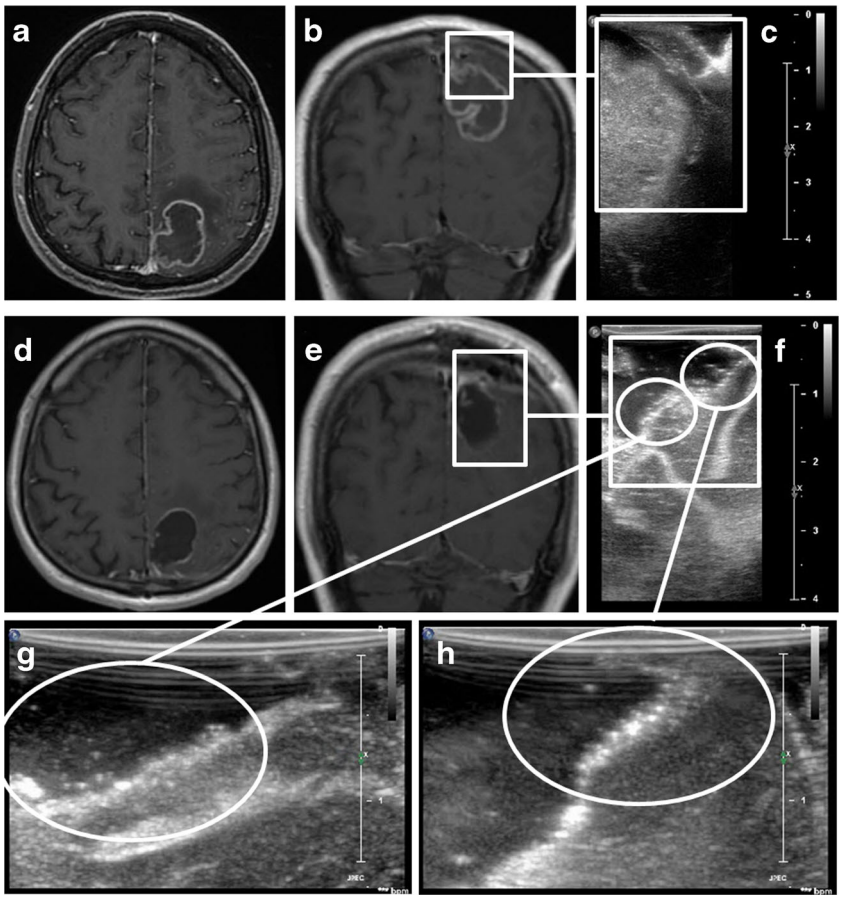

Fig. 1 Intraoperative ultrasound imaging in an illustrative case. **a**, **b** Preoperative T1-weighted gadolinium-enhanced magnetic resonance (MR) images show a ring-enhancing parietal mass. **c** Transdural intraoperative ultrasound (ioUS) imaging before the resection in a coronary plane shows the lesion to be homogenously hyperechogenic, even in MR-hypointense, non-enhancing areas. **d**, **e** Postoperative T1-weighted gadolinium-enhanced MR images and a corresponding postresection ioUS surface scan (**f**) in a coronary plane. **g**, **e** Intracavital ioUS scanning of the resection cavity shows a complete resection

in those patients without ioUS ($n=28$) was 18.8 months (95 % CI 15.8–NA) and 20 patients died (see Table 2). After fitting the Cox proportional hazards model to all patients, adjusting for age, preoperative KPS, tumor volume, and 5-ALA, we found a lower hazard for "death" in the group of glioblastoma patients with ioUS (hazard ratio = 0.62; 95 % CI 0.32–1.24; $p=0.180$), however not statistically significant (see Table 3).

Secondary endpoint—PFS

Prolonged PFS was seen for the ioUS cohort as depicted in a graphical approach (Fig. 3b). Median PFS in the ioUS group was 7.1 months (95 % CI 5.6–11.7 months) compared to patients operated without the use of ioUS (median PFS 3.4 months; 95 % CI 3.4–11.2 months; see Table 2). The estimated hazards ratio for ioUS versus no ioUS was 0.59

Table 1 Basic patient characteristics

	All	ioUS	w/o ioUS	*p* value
n	76	48	28	
Sex (m/f)	46/30	30/18	16/12	0.808[b]
Age (years)	57.4 ± 11.6	58.0 ± 12.6	56.5 ± 9.6	0.447[c]
Tumor volume (mm^3)	47,534	50,822	42,016	0.540[c]
Cortex-to-core distance (mm)	22.6 ± 8.9	23.1 ± 8.8	22.0 ± 9.3	0.418[c]
Preop KPS (%)[a]	80 (70–87.5)	80 (70–80)	80 (70–90)	0.090[c]
3m postop KPS (%)[a]	80 (70–90)	80 (60–90)	80 (70–90)	0.541[c]
Surgery duration (h)	3.7 ± 1.5	3.6 ± 1.5	4.1 ± 1.3	0.065[c]

ioUS intraoperative ultrasound, *w/o* without, *KPS* Karnofsky performance status

[a] Preoperative Karnofsky performance status scale as median (interquartile range)

[b] Fisher's exact test

[c] Mann-Whitney *U* test

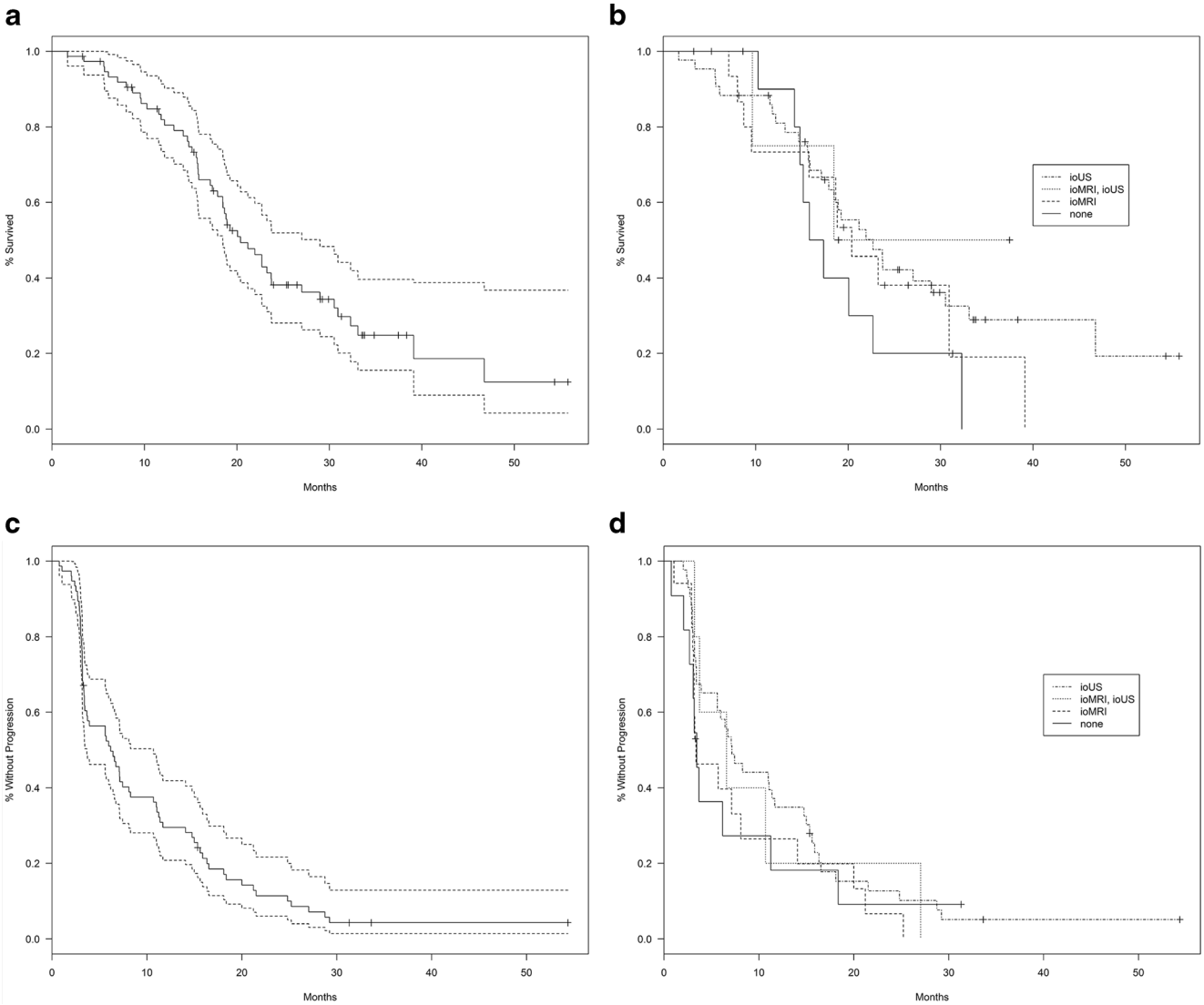

Fig. 2 Kaplan-Meier plots showing overall survival (OS) (**a**) and progression-free survival (PFS) (**c**) in all glioblastoma patients ($n = 76$) including the 95 % confidence intervals (*dashed lines*). OS (**b**) and PFS (**d**) of all patients depending on the intraoperative resection control device used

(95 % CI 0.33–1.05; $p = 0.072$) when adjusting for the set of confounders (see Table 3).

Additional analyses

We performed additional analyses in order to assess whether the more favorable results regarding OS and PFS in glioblastoma patients operated with ioUS compared to glioblastoma patients operated without ioUS are explained by different preoperative tumor volumes or due to different postoperative treatment (chemotherapy and/or radiation). Mean preoperative tumor volume within the ioUS group ($n = 48$) was 50,822 mm^3 (interquartile range (IQR), 7789–81,325 mm^3), and mean tumor volume in glioblastoma patients operated without ioUS ($n = 28$) was 42,016 mm^3 (IQR, 14,700–56,089 mm^3). There was no statistical significant difference between both groups ($p = 0.540$; Mann-Whitney U test). In addition, we looked at the postoperative treatment modalities following microsurgical complete resection in the glioblastoma group (shown in Table 4). Both, the ioUS group and the group of patients without ioUS had a similar distribution of treatment modalities with a rate of 83 % and 82 % of patients treated with a combined regimen (any chemotherapy at any time point during disease course and radiotherapy). There was no significant statistical difference between the ioUS group and the non-ioUS group regarding this distribution ($p = 0.852$; two-sided Fisher's exact test). Also, the groups did not differ regarding the rate of patients that received standard therapy

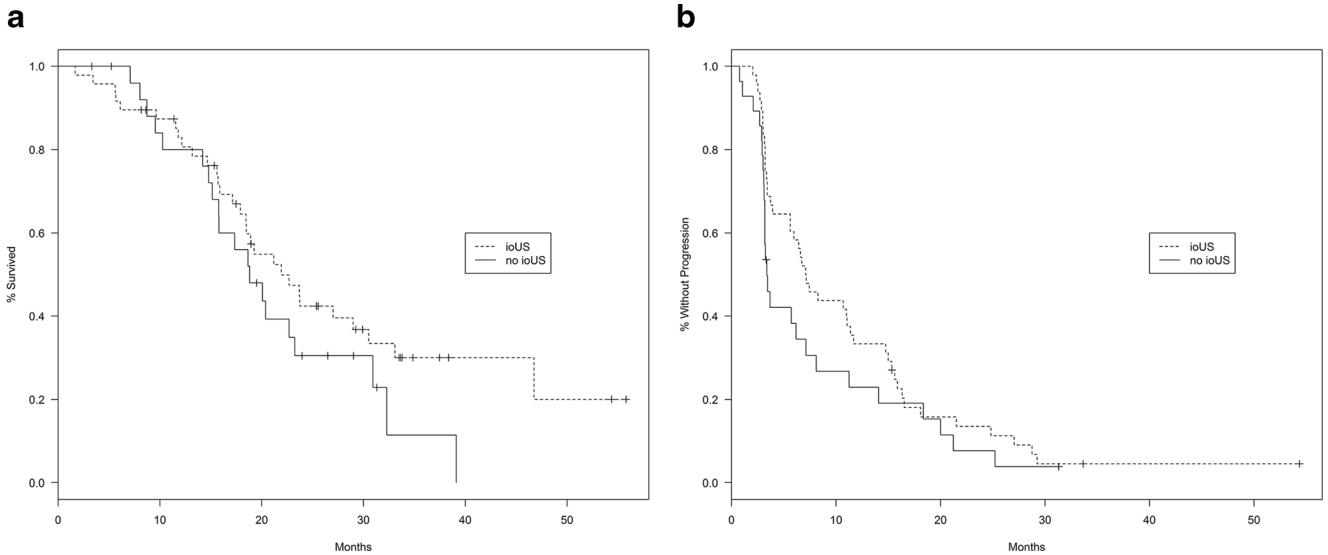

Fig. 3 Kaplan-Meier plots showing overall survival (OS) (**a**) and progression-free survival (PFS) (**b**) comparing the intraoperative ultrasound (ioUS) group and the group operated without ioUS

(radiotherapy plus concomitant and adjuvant temozolomide) as first-line treatment ($p = 0.306$, chi-squared test; see Table 4) nor regarding cumulative radiation doses ($p = 0.546$, Mann-Whitney U test).

We also looked at the distribution of the molecular markers isocitrate dehydrogenase (IDH1) R132H mutation and O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation. IDH1 R132H mutation status was assessed in 41 patients, and none of the tested individuals was found to carry the R132H point mutation—as expected in primary glioblastoma. MGMT promotor methylation status was assessed in 52 patients. In 11/52 patients, the MGMT promotor was methylated (nine patients in the ioUS group and two patients in the non-ioUS group). The difference between the groups regarding MGMT methylation status was not statistically significant ($p = 0.431$; two-sided Fisher's exact test) (see also Table 4).

Table 2 Primary and secondary end points

Devices	*n*	Events	Median	95 % CI
		(months)	(months)	
OS				
Overall	76	50	20.4	18.5–29.0
ioUS	48	30	21.9	18.5–33.1
w/o ioUS	28	20	18.8	15.8–NA
PFS				
Overall	76	71	6.2	3.7–10.7
ioUS	48	45	7.1	5.6–11.7
w/o ioUS	28	26	3.4	3.4–11.2

CI confidence interval, *OS* overall survival, *ioUS* intraoperative ultrasound, *w/o* without, *PFS* progression-free survival

Discussion

Primary endpoint

In this study, OS and PFS were longer in glioblastoma patients that had a GTR using ioUS compared to those patients without ioUS. In a Cox model, this difference did not reach statistical significance. However, a trend toward a benefit of ioUS use can be seen, especially concerning PFS. Regarding glioblastoma, it is known that the tumor burden goes well beyond the contrast-enhancing part seen on MRI. Recent positron emission tomography (PET) studies showed that glioblastoma tumor volume is usually greater when assessed with PET

Table 3 Results of the Cox proportional hazards model for OS and PFS

Variable	HR	95 % CI	*p* value
OS			
ioUS	0.63	0.31–1.24	0.18
5-ALA	0.71	0.33–1.48	0.35
Log (volume)	1.06	0.84–1.32	0.64
Age	1.03	1.0–1.06	0.03
KPS (preop)	0.75	0.84–1.32	0.80
PFS			
ioUS	0.59	0.33–1.05	0.07
5-ALA	0.58	0.31–1.06	0.08
Log (volume)	1.10	0.89–1.35	0.37
Age	1.01	0.99–1.04	0.15
KPS (preop)	1.57	0.21–1.35	0.66

OS overall survival, *PFS* progression-free survival, *HR* hazard ratio, *CI* confidence interval, *ioUS* intraoperative ultrasound, *5-ALA* 5-aminolevulinic acid, *w/o* without, *KPS* Karnofsky performance status

Table 4 Distribution of initial postoperative treatment modalities (chemotherapy, radiotherapy, combined radio-chemotherapy) after microsurgical glioblastoma complete resection

Postop treatment	ioUS ($n=48$)	No ioUS ($n=28$)	Total ($n=76$)	p value
None	0	1	1	
Chemotherapy alone	3	2	5	
Radiotherapy alone	5	2	7	
RT and chemotherapy[a]	40	23	63	0.852[b]
➜ Standard therapy (RT with concomitant and adjuvant TMZ)	32	22	54	0.306[c]
Cumulative radiation dose in Gray [mean(range)]	55.8 (39–60)	57.6 (35–60)	56.4 (35–60)	0.546[d]
MGMT status				
Methylated	9	2	11	
Not methylated	15	9	24	
Unknown	24	17	41	0.431[b]

ioUS intraoperative ultrasound, *RT* radiotherapy, *TMZ* temozolomide

[a] Any chemotherapy at any time during disease course

[b] Two-sided Fisher's exact test

[c] Two-sided chi-square test

[d] Mann-Whitney *U* test

compared to gadolinium-enhanced MRI [2, 10, 11]. By convention, the EOR in glioblastoma is calculated by defining all contrast-enhancing tumor volume as 100 %. Of course, even removing all contrast-enhancing tumor parts (100 % by conventional definition) does not mean that all tumor cells have been removed. None-enhancing parts at the border zones frequently remain. These non-enhancing tumor parts are not detected using standard gadolinium-enhanced ioMRI sequences since ioMRI resection control is classically based on contrast enhancement alone. On the contrary, it is well known that low-grade gliomas (usually non-enhancing lesions) are well delineated with ioUS [14]. In fact, we propose that glioblastoma resections with ioUS go beyond the contrast-enhancing parts, enabling a more complete removal of the tumor (supratotal resection), which is one of the possible reasons for the effects of ioUS on OS and PFS that we observed. The same effect, fluorescence beyond MRI contrast enhancement was recently shown for 5-ALA [24].

Intraoperative resection control devices

IoMRI was introduced in the late 1990s starting with a 0.5-T low-field "double-doughnut system" [4]. High-field ioMRI (1.5–3.0 T) was started later—the choice between the two setups is usually a tradeoff between image quality and integration into the clinical workflow as well as costs [12]. In our series, an intraoperative low-field system was used as described in detail above and published previously [3, 5]. In a randomized controlled trial by Senft et al. assessing the role of ioMRI in brain tumor surgery, a total of 58 patients were included and 29 patients (22 glioblastomas) were randomly allocated to the intraoperative ultra-low-field MRI group (same ioMRI system that was used in this study) [25]. Patients operated with ioMRI had longer PFS (226 vs. 154 days), but this difference did not reach statistical significance ($p=0.083$). It is difficult to compare studies like this to our own results, since we purposely included only patients with complete resections and since we mainly focused on OS instead of PFS. When looking at EOR, it has to be taken into account that ioMRI has a huge intrinsic advantage over all other guidance modalities: It is the very same modality that is used to evaluate EOR postoperatively (usually high-field early postoperative MRI). However, it is questionable whether this judgment (contrast enhancement on MRI) is a fair estimate of glioblastoma tumor burden, since it is well known that non-enhancing tumor zones are present in addition to the contrast-enhancing core [34].

5-ALA is a precursor in the biosynthesis of heme that accumulates in malignant gliomas. It carries fluorescent properties that make tumor tissue better visible to the surgeon when using a specially modified microscope [27]. In our series, 5-ALA and ioUS had similar effects on OS and PFS. However, our 5-ALA group was very small ($n=19$) and we did not look at all glioblastoma cases up-front, but only at those who had GTR. Moreover, the phase III randomized controlled trial by Stummer et al. (2006) found a difference in PFS, but not for OS which is in accordance to our results [28]. Since 5-ALA fluorescence is based on metabolic effects rather than blood-brain barrier breakdown (as in gadolinium-enhanced ioMRI), using 5-ALA certainly adds additional information and, like ioUS, has the advantage of real-time and low-cost imaging. However, ioUS might be especially useful in glioblastoma patients with no active 5-ALA fluorescence.

IoUS is a rather old technology introduced in the 1960s that was not used frequently over a long period of time due to suboptimal image quality. However, in recent years, ioUS had a comeback mainly because of technical improvements (reduced probe size, improved resolution with high-frequency probes, and the option of 3D imaging) [6, 26, 33]. In brain tumor surgery, ioUS has been shown to be especially helpful in surgery for cystic gliomas [9]. In addition, ioUS can be combined with neuronavigation resulting in improved orientation [15, 19] and it can add valuable information on the vasculature during tumor surgery [21, 32]. The data on ioUS in glioblastoma surgery is still very limited. Coburger et al. recently compared navigated high-resolution linear array intraoperative ultrasound (lioUS) to conventional intraoperative ultrasound (cioUS) in a prospective cohort of 15 glioblastoma patients and 44 resection sites. LioUS (L15-7 probe that was also used in this study) detected residual tumor after microsurgical complete resection in all cases and in 33 of 44 sites (75 %). Histopathology workup revealed solid tumor in 66 % and infiltration zone in 34 % of the cases—there were no false-positive or false-negative findings [8]. A group from Trondheim could show that survival after glioblastoma surgery significantly improved within the same period that ultrasound and neuronavigation were introduced in their department [22]. However, this was just a pure observation without any detailed analyses. This is the first analysis that looks at the influence of ioUS on OS and PFS in glioblastoma. Advantages of ioUS over ioMRI are obviously low costs as well as the fact that images can be obtained repeatedly and fast, whereas ioMRI is usually obtained once at the end of the resection because of the time delay.

Neuronavigation was used in all cases of our series. It cannot incorporate intraoperative anatomic changes (e.g., brain shift), for it does not provide real-time information [20]. However, it should be evaluated whether navigated ioUS with preoperative or intraoperative MRI images leads to improvements in both EOR and safety as well as patient outcome, especially when used by surgeons without long-standing experience with ioUS.

Limitations

We are fully aware of some limitations that are associated with the retrospective design of this study and with the limited number of patients. Since in some patients, more than one resection control modality was used and since subgroups are rather small, it is impossible to study the effect of each device. However, the main analysis looking at ioUS usage is based on two clearly separated groups without any overlap. Due to the retrospective design, it is not possible to judge post hoc whether GTR was intended by the surgeon. Therefore, the intraoperative resection control devices cannot be linked to EOR or to survival in general. However, this information is not necessary with regard to our research question (Is the outcome of patients who had GTR dependent on the intraoperative resection device used?). It is also possible that there might be a bias due to the personal preferences of each surgeon. For instance, it might be possible that one surgeon preferred ioMRI, whereas another surgeon chose ioUS more frequently. One could argue that intraoperative high-frequency ultrasound is preferentially used for superficial lesions since higher frequency leads usually to enhanced axial resolution at the expense of tissue penetration. However, the distance between the core of the lesion and the closest cortical surface was comparable between both groups (see Table 1). In addition, in our institution, high-frequency ioUS is routinely used for deep lesions. Due to the reduction of probe sizes in recent years, ioUS probes can be introduced into the resection cavity as described by Serra et al. (2012). Thus, the ioUS cohort is not a selection of superficial supposedly more favorable cases.

Conclusion

Glioblastoma patients who had GTR have prolonged OS and PFS if ioUS was used. Larger studies (ideally multicenter and randomized) should compare ioMRI to ioUS and confirm these findings with greater statistical power. At this point, routine experienced use of ioUS in microsurgical resections of glioblastomas is recommended. Experienced use of modern ioUS remains a competitive intraoperative imaging device in glioblastoma surgery.

Compliance with ethical standards

Conflict of interest None

References

1. Albert FK, Forsting M, Sartor K, Adams HP, Kunze S (1994) Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis. Neurosurgery 34:45–60, **discussion 60–41**
2. Arbizu J, Tejada S, Marti-Climent JM, Diez-Valle R, Prieto E, Quincoces G, Vigil C, Idoate MA, Zubieta JL, Penuelas I, Richter JA (2012) Quantitative volumetric analysis of gliomas with sequential MRI and (1)(1)C-methionine PET assessment: patterns of integration in therapy planning. European journal of nuclear medicine and molecular imaging 39:771–781. doi:10.1007/s00259-011-2049-9
3. Bellut D, Hlavica M, Muroi C, Woernle CM, Schmid C, Bernays RL (2012) Impact of intraoperative MRI-guided transsphenoidal surgery on endocrine function and hormone substitution therapy in patients with pituitary adenoma. Swiss medical weekly 142: w13699. doi:10.4414/smw.2012.13699

4. Black PM, Moriarty T, Alexander E 3rd, Stieg P, Woodard EJ, Gleason PL, Martin CH, Kikinis R, Schwartz RB, Jolesz FA (1997) Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications. Neurosurgery 41:831–842, **discussion 842–835**
5. Burkhardt JK, Neidert MC, Woernle CM, Bozinov O, Bernays RL (2013) Intraoperative low-field MR-guided frameless stereotactic biopsy for intracerebral lesions. Acta neurochirurgica 155:721–726. doi:10.1007/s00701-013-1639-7
6. Burkhardt JK, Serra C, Neidert MC, Woernle CM, Fierstra J, Regli L, Bozinov O (2014) High-frequency intra-operative ultrasound-guided surgery of superficial intra-cerebral lesions via a single-burr-hole approach. Ultrasound in medicine & biology. doi:10.1016/j.ultrasmedbio.2014.01.024
7. Burkhardt JK, Serra C, Neidert MC, Woernle CM, Fierstra J, Regli L, Bozinov O (2014) High-frequency intra-operative ultrasound-guided surgery of superficial intra-cerebral lesions via a single-burr-hole approach. Ultrasound in medicine & biology 40:1469–1475. doi:10.1016/j.ultrasmedbio.2014.01.024
8. Coburger J, Konig RW, Scheuerle A, Engelke J, Hlavac M, Thal DR, Wirtz CR (2014) Navigated high frequency ultrasound: description of technique and clinical comparison with conventional intracranial ultrasound. World neurosurgery 82:366–375. doi:10.1016/j.wneu.2014.05.025
9. Enchev Y, Bozinov O, Miller D, Tirakotai W, Heinze S, Benes L, Bertalanffy H, Sure U (2006) Image-guided ultrasonography for recurrent cystic gliomas. Acta neurochirurgica 148:1053–1063. doi:10.1007/s00701-006-0858-6, **discussion 1063**
10. Galldiks N, Ullrich R, Schroeter M, Fink GR, Jacobs AH, Kracht LW (2010) Volumetry of [(11)C]-methionine PET uptake and MRI contrast enhancement in patients with recurrent glioblastoma multiforme. European journal of nuclear medicine and molecular imaging 37:84–92. doi:10.1007/s00259-009-1219-5
11. Idema AJ, Hoffmann AL, Boogaarts HD, Troost EG, Wesseling P, Heerschap A, van der Graaf WT, Grotenhuis JA, Oyen WJ (2012) 3'-Deoxy-3'-18F-fluorothymidine PET-derived proliferative volume predicts overall survival in high-grade glioma patients. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 53:1904–1910. doi:10.2967/jnumed.112.105544
12. Kubben PL, ter Meulen KJ, Schijns OE, ter Laak-Poort MP, van Overbeeke JJ, van Santbrink H (2011) Intraoperative MRI-guided resection of glioblastoma multiforme: a systematic review. The lancet oncology 12:1062–1070. doi:10.1016/S1470-2045(11)70130-9
13. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R (2001) A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. Journal of neurosurgery 95:190–198. doi:10.3171/jns.2001.95.2.0190
14. Le Roux PD, Berger MS, Wang K, Mack LA, Ojemann GA (1992) Low grade gliomas: comparison of intraoperative ultrasound characteristics with preoperative imaging studies. Journal of neuro-oncology 13:189–198
15. Miller D, Heinze S, Tirakotai W, Bozinov O, Surucu O, Benes L, Bertalanffy H, Sure U (2007) Is the image guidance of ultrasonography beneficial for neurosurgical routine? Surgical neurology 67:579–587. doi:10.1016/j.surneu.2006.07.021, **discussion 587–578**
16. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, Duncan G, Skingley P, Foster G, Levine M (1996) A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 78:1470–1476
17. Ohgaki H, Kleihues P (2005) Epidemiology and etiology of gliomas. Acta neuropathologica 109:93–108. doi:10.1007/s00401-005-0991-y
18. Paek SH, Audu PB, Sperling MR, Cho J, Andrews DW (2005) Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. Neurosurgery 56:1021–1034, **discussion 1021–1034**
19. Rasmussen IA Jr, Lindseth F, Rygh OM, Berntsen EM, Selbekk T, Xu J, Nagelhus Hernes TA, Harg E, Haberg A, Unsgaard G (2007) Functional neuronavigation combined with intra-operative 3D ultrasound: initial experiences during surgical resections close to eloquent brain areas and future directions in automatic brain shift compensation of preoperative data. Acta neurochirurgica 149:365–378. doi:10.1007/s00701-006-1110-0
20. Roberts DW, Hartov A, Kennedy FE, Miga MI, Paulsen KD (1998) Intraoperative brain shift and deformation: a quantitative analysis of cortical displacement in 28 cases. Neurosurgery 43:749–758, **discussion 758–760**
21. Rygh OM, Nagelhus Hernes TA, Lindseth F, Selbekk T, Brostrup Muller T, Unsgaard G (2006) Intraoperative navigated 3-dimensional ultrasound angiography in tumor surgery. Surgical neurology 66:581–592. doi:10.1016/j.surneu.2006.05.060, **discussion 592**
22. Saether CA, Torsteinsen M, Torp SH, Sundstrom S, Unsgard G, Solheim O (2012) Did survival improve after the implementation of intraoperative neuronavigation and 3D ultrasound in glioblastoma surgery? A retrospective analysis of 192 primary operations. Journal of neurological surgery Part A, Central European neurosurgery 73:73–78. doi:10.1055/s-0031-1297247
23. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS (2011) An extent of resection threshold for newly diagnosed glioblastomas. Journal of neurosurgery 115:3–8. doi:10.3171/2011.2.JNS10998
24. Schucht P, Knittel S, Slotboom J, Seidel K, Murek M, Jilch A, Raabe A, Beck J (2014) 5-ALA complete resections go beyond MR contrast enhancement: shift corrected volumetric analysis of the extent of resection in surgery for glioblastoma. Acta neurochirurgica 156:305–312. doi:10.1007/s00701-013-1906-7, **discussion 312**
25. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V (2011) Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. The lancet oncology 12:997–1003. doi:10.1016/S1470-2045(11)70196-6
26. Serra C, Stauffer A, Actor B, Burkhardt JK, Ulrich NH, Bernays RL, Bozinov O (2012) Intraoperative high frequency ultrasound in intracerebral high-grade tumors. Ultraschall in der Medizin 33:E306–312. doi:10.1055/s-0032-1325369
27. Stummer W, Kamp MA (2009) The importance of surgical resection in malignant glioma. Current opinion in neurology 22:645–649. doi:10.1097/WCO.0b013e3283320165
28. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, Group AL-GS (2006) Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. The lancet oncology 7:392–401. doi:10.1016/S1470-2045(06)70665-9
29. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T, Group AL-GS (2008) Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 62:564–576. doi:10.1227/01.neu.0000317304.31579.17, **discussion 564–576**
30. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO, European Organisation for R, Treatment of Cancer Brain T, Radiation Oncology G, National Cancer Institute of Canada Clinical Trials G (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in

glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. The lancet oncology 10:459–466. doi:10.1016/S1470-2045(09)70025-7

31. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO, European Organisation for R, Treatment of Cancer Brain T, Radiotherapy G, National Cancer Institute of Canada Clinical Trials G (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. The New England journal of medicine 352:987–996. doi:10.1056/NEJMoa043330
32. Sure U, Benes L, Bozinov O, Woydt M, Tirakotai W, Bertalanffy H (2005) Intraoperative landmarking of vascular anatomy by integration of duplex and Doppler ultrasonography in image-guided surgery. Technical note Surgical neurology 63:133–141. doi:10.1016/j.surneu.2004.08.040, **discussion 141–132**
33. Ulrich NH, Burkhardt JK, Serra C, Bernays RL, Bozinov O (2012) Resection of pediatric intracerebral tumors with the aid of intraoperative real-time 3-D ultrasound. Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery 28:101–109. doi:10.1007/s00381-011-1571-1
34. Yamahara T, Numa Y, Oishi T, Kawaguchi T, Seno T, Asai A, Kawamoto K (2010) Morphological and flow cytometric analysis of cell infiltration in glioblastoma: a comparison of autopsy brain and neuroimaging. Brain tumor pathology 27:81–87. doi:10.1007/s10014-010-0275-7
35. Yoo H, Kim YZ, Nam BH, Shin SH, Yang HS, Lee JS, Zo JI, Lee SH (2009) Reduced local recurrence of a single brain metastasis through microscopic total resection. Journal of neurosurgery 110:730–736. doi:10.3171/2008.8.JNS08448
36. Zinn PO, Colen RR, Kasper EM, Burkhardt JK (2013) Extent of resection and radiotherapy in GBM: a 1973 to 2007 surveillance, epidemiology and end results analysis of 21,783 patients. International journal of oncology 42:929–934. doi:10.3892/ijo.2013.1770

Comments

Miguel A. Arraez, Malaga, Spain

The article from Dr. M. Neidert and co-workers "Influence of intraoperative resection control modalities on survival following gross total resection of glioblastoma" deserves interest. It is clear that the current aspects of glioma surgery are presided by the interest about impact of radical resection on survival and also about which intraoperative technologies can be able to achieve the following goal: maximal resection without increased morbidity. The majority of the recent published articles are referred to the use of intraoperative MRI and 5-ALA. No much attention has been paid to the use of intraoperative ultrasonography as a tool to safely increase resection and survival. It is interesting the conclusion of the authors stating that the use of ultrasonography associated or not to intraoperative MRI increases survival and also quality of life according to the KPS. The increased resection leading to prolonged survival has been recently linked to the resection not only of the uptaking ring of contrast but also to the resection of T2 abnormal MRI signal and also to the pinky (non-intense) 5-ALA fluorescent peripheral area of the tumor. This could be the explanation about how ultrasonography could improve survival: identifying and enabling the resection of the peripheral non-contrast-enhanced infiltrating tumor. Regarding the safety of the technique, we consider a potential limitation what in our modest experience is a drawback for ultrasonography: the difficulty to define the margin of the tumor (even more, if we deal with the infiltrating non-contrast component). I do agree with the authors about the need of further studies with a larger series of patients in order to clarify the usefulness of intraoperative ultrasonography as surgical adjunct to improved tumor resection and survival in glioma surgery.

Jan Regelsberger, Hamburg, Germany

The paper by Neidert et al. presents an interesting topic with the influence of different intraoperative imaging tools on survival on primary glioblastomas. The study was designed whether OS and PFS might depend on the intraoperative techniques achieving GTR which was confirmed by post-op MRI serving as the main inclusion criteria. Glioblastoma resected by ioUS turned out to be associated with prolonged OS and PFS.

Intraoperative ultrasound (ioUS) has been focused in many studies but has been less noticed in times of 5-ALA which is serving at present as the gold standard achieving GTR and thus improving overall survival in GBM patients. Outstanding technical developments have been made in the sonographic field, not aiming for neurosurgical purposes but finally convincing the need to reevaluate the power of ioUS. This has been done by Neidert et al. where IOUS turned out to be superior to intraoperative MRI (ioMR) where non-enhancing tumor parts are well delineated sonographically and ultrasound-guided resection goes beyond the contrast-enhancing parts which is shown by extended OS and PFS. Therefore, intraoperative sonography should be noticed as an important tool especially in those GBM patients without 5-ALA enhancement.

One may not forget that technical limitations are still obvious where tumor infiltration zones cannot be distinguished from edema, low-grade tumor portions, or irregularities according to the surgical manipulation. In addition, one may assume that this is a retrospective and small series including a certain overlap between the groups where statistical analyses were used to separate ioUS patients from those without. After all, it is still left unanswered if any combination of these three techniques (ioUS vs. ioMRI vs. 5-ALA) is superior to a single intraoperative modality.

As intraoperative imaging tools (and standardized radiochemotherapy in primary GBM) have improved the clinical course of these patients, neurophysiological monitoring is introduced to improve the functional results but may contradict our efforts for GTR where surgical resection may be stopped early when residual tumor is still visible and reduced potentials admonish to go further. In this light, "better seeing" by using ioUS is a great (and especially less expensive technique compared to MRI) advantage which is worthwhile to be further investigated and advertised.